small animal - is readable on the prior art host. Only amendment of a distinctive host not readable on the prior art will obviate this rejection." The Chemical Abstracts reference cited in the rejection refers only to the rat as an example of a small animal. This is true also of British Specification 2101114 (copy enclosed) from which the Abstract derived.

In these circumstances, to draw an absolutely clear line of distinction between the present invention and the prior art, new claim 5 now specifies that the small mammal is a dog or cat (cf. claim 2). Claims 2 and 4 have been cancelled as redundant and a consequential amendment has been made in claim 3. It is believed, in these circumstances, that the amended claims are clearly distinguished from the prior art and relate to a utility which the Examiner agrees was not taught in the art.

Favorable reconsideration and allowance of the application with withdrawal of the final rejection are therefore believed to be in order and are earnestly requested.

Should minor issues remain which can be resolved by means of a telephone interview, the Examiner is respectfully requested to contact the undersigned attorney at the below-listed telephone number in order to resolve said issues.

In the event that this paper is not considered to be timely filed, applicants hereby petition for an appropriate extension of time. The fee for any such extension may be

charged to our Deposit Account No. 01-2395, along with any other required fees.

Respectfully submitted,

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Attachment: Copy of British Specification 2101114

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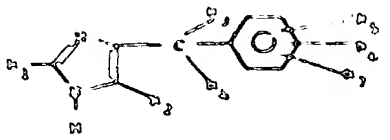
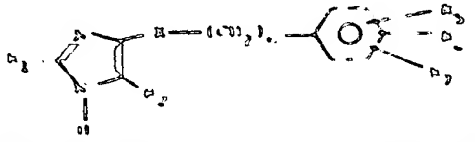
(54) **Substituted imidazole derivatives and their preparation and use**

(57) Mainly novel compounds of the formula



(I)

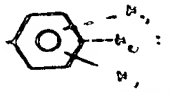
or



(II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or CH_2OH, R_2 is H or CH_3, R_3 is

CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)CH_3$, $CH_2CH_2CH_2CH_3$,

$-CH_2CH(CH_3)CH_3$, or 

and R_4 is H or OH; or R_3 and R_4 together represent CH_2, $CH(CH_3)$, $CH(CH_2CH_3)$, $-CH(CH_3)-CH_2-CH_2-$, $-C(CH_3)(CH_3)-CH_2-$ or $-CH(CH_2CH_2CH_3)-$;

X is $-CH(R_9)-CH(R_9)-$ or $-C(R_{11})=C(R_{10})-$;

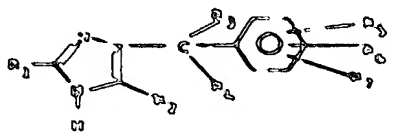
R_9, R_9 and R_7, which can be the same or different, are H, CH_3, CH_2CH_3, halogen, OH or $-OCH_3$ or R_9 is hydrogen and R_9 and R_7 together form an $-O-CH_2-O-$bridge between two adjacent carbon atoms in the phenyl group, $-CHR_8-$ is $-CH_2-$, $-CH(CH_3)-$, $-CH(CH(CH_3)CH_3)-$, $-CH(CH_2CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_2-CH_3)-$, $-CH(CH_2CH_2CH_2CH_2CH_3)-$ or $>C(CH_2)-$, $-C(CH_3)=CH-$, $>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$, or $>C=CH-CH_2CH_2CH_3$; R_8 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, CH_3, CH_2CH_3, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $CH_2CH_2CH_2CH_3$; R_{11} is H, CH_3, CH_2CH_3, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$; n is 0 to 4; and their non-toxic pharmaceutically acceptable acid addition salts exhibit antihypertensive.

GB 2 101 114

Substituted imidazole derivatives and their preparation and use

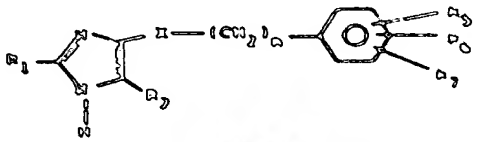
The present invention relates to substituted imidazole derivatives and their non-toxic, pharmaceutically acceptable acid addition salts, and their preparation, to pharmaceutical compositions containing the same, and to their use.

The imidazole derivatives of the present invention have the general formula



(I)

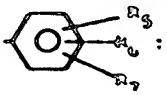
or



(II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or $-CH_2OH$; R_2 is H or CH_3; R_3 is

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$

$-CH_2CH=CH_2$, or  ; and

R_4 is H or OH; or R_3 and R_4 together represent

$=CH_2$, $=CH-CH_3$, $=CH-CH_2CH_3$,

$=C(CH_3)-CH_3$, or $=CH-CH_2CH_2CH_3$;

X is $-CH(R_8)-CH(R_9)-$ or $-C(R_{11})=C(R_{10})-$;

R_5, R_6 and R_7, which can be the same or different are H, $-CH_3$, $-CH_2CH_3$, halogen, OH or $-OCH_3$ or R_5 is hydrogen and R_6 and R_7 together form an $-O-CH_2-O-$ bridge between two adjacent carbon atoms in the phenyl group;

$-CHR_8-$ is $-CH_2-$, $-CH(CH_3)-$, $-CH(-CH_2CH_3)-$,

$-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)-CH_3)-$, $-CH(-CH_2CH_2CH_2CH_3)-$

or $>C=CH_2$, $>C=CH-CH_3$, $>C=CH-CH_2CH_3$, $>C=C(CH_3)-CH_3$,

$>C=CH-CH_2CH_2CH_3$, R_9 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$,

$-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, $-CH_3$,

$-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$;

R_{11} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$;

then R_6, R_8 and R_7 are not all simultaneously hydrogen;

– when R_{11}, R_7 and R_8 are all hydrogen and R_5 is 

then R_6, R_8, R_7 are not all simultaneously hydrogen.

– R_6 and R_8 are not simultaneously hydrogen, and

– R_{11} and R_{10} are not simultaneously hydrogen.

Because of the tautomerism in the imidazole ring the compounds of the general formula I and II are 4(5)-substituted imidazole derivatives.

The non-toxic pharmaceutically acceptable acid addition salts of these compounds are also within the scope of the invention.

The compounds of the formula (I) and (II) form acid addition salts with both organic and inorganic acids. They can thus form many pharmaceutically usable acid addition salts, eg. for instance chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, citrates, benzoates, salicylates, ascorbates and the like.

The invention includes within its scope pharmaceutical compositions comprising at least one of the compounds of formula (I) or (II) or a nontoxic, pharmaceutically acceptable salt thereof and a compatible pharmaceutically acceptable carrier therefor.

The invention provides, for example, the following specific compounds of formula (I)

4-[α,α-bis(2-methylphenyl)hydroxymethyl]imidazole
4-[(α-(2-methylphenyl)]-2-methylbenzyl]imidazole
4-[(α-phenylbenzyl)-5-methylimidazole
4-[(α-(2,6-dimethylphenyl)]-(α-methyl)hydroxymethyl]imidazole
4-[(α-(2,3-dimethylphenyl)]-(α-methyl)hydroxymethyl]imidazole
4-[α,α-bis(2-methylphenyl)hydroxymethyl]-5-methylimidazole
4-[(α-(2-methylphenyl)]-2-methylbenzyl]-5-methylimidazole
4-[(α-methyl)-2,6-dimethylbenzyl]imidazole
4-[(α-methyl)-2,3-dimethylbenzyl]imidazole
4-[(α-ethyl)-3-methylbenzyl]imidazole
4-[(α-butyl)-2,3-dimethylbenzyl]imidazole
4-[(α-methyl)-2,3-dimethylbenzyl]-2-methylimidazole
4-[(α-propyl)-2-methylbenzyl]imidazole
4-[(α-methyl)-2-methylbenzyl]imidazole
4-[(α-methyl)-2,5-dimethylbenzyl]imidazole
4-[α-ethyl-α-(3-methylphenyl)-hydroxymethyl]imidazole
4-[α-butyl-α-(2,3-dimethylphenyl)-hydroxymethyl]imidazole
4-[α-methyl-α-(2,3-dimethylphenyl)-hydroxymethyl]-2-methylimidazole
4-[α-propyl-α-(2-methylphenyl)-hydroxymethyl]imidazole
4-[α-methyl-α-(2-methylphenyl)-hydroxymethyl]imidazole
4-[α-methyl-α-(2,5-dimethylphenyl)-hydroxymethyl]imidazole
4-[α,α-bis-(2,3-dimethylphenyl)hydroxymethyl]imidazole
4-[α-(2,3-dimethylphenyl)-2,3-dimethylbenzyl]imidazole
4-[(α-ethyl)-2,6-dimethylbenzyl]imidazole
4-[(α-ethyl)-2,3-dimethylbenzyl]imidazole
1-(4-imidazolyl)-1-(2,3-dimethylphenyl)ethylene
1-(4-imidazolyl)-1-(2,6-dimethylphenyl)ethylene

The following specific compounds of formula (II):

4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole
4-[2-(2,6-dimethylphenyl)propyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-methylpropyl]imidazole
4-[2-(2,6-dimethylphenyl)-2-hydroxyethyl]imidazole
4-(2-phenylpropyl)imidazole
4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-propenyl]imidazole
4-(2-methyl-4-phenyl-1-butenyl)imidazole
4-[2-(4-chlorophenyl)-1-methylpropyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]imidazole
4-[3-(2,6-dimethylphenyl)-2-methyl-1-propenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-ethylethenyl]imidazole

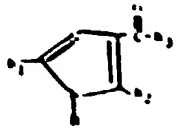
4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-5-methylimidazole
4-[2-(2,6-dichlorophenyl)-1-methylethenyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]imidazole
4-[3-(2,6-dimethylphenyl)-1-ethyl-1-propenyl]imidazole
4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]-5-methylimidazole
4-[5-(2,6-dimethylphenyl)-1-methylpentyl]imidazole
4-[4-(2,6-dichlorophenyl)-1-methyl-1-butenyl]imidazole
4-[2-(2,6-dimethylphenyl)-1-ethylethyl]imidazole
4-[2-(2,6-dimethylphenyl)-2-ethylethyl]imidazole
4-[2-(3,4-methylenedioxyphenyl)propyl]imidazole

The compounds of the present invention have been found to possess excellent antihypertensive activity. Preliminary tests have shown that they also possess other valuable pharmacological properties, for example, antithrombotic effect. Antimycotic and antifungal properties have also been found.

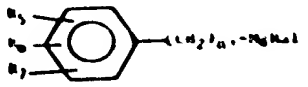
While all of the compounds of formula (I) and (III) essentially satisfy the objectives of the present invention, certain groups of compounds remain preferred. One such preferred group is represented by formula III wherein R_4 is hydrogen, R_3 is alkyl and R_5, R_6 and R_7, which can be the same or different, each are hydrogen, methyl, ethyl or halogen. Another preferred group of compounds is represented by formula III, wherein R_5, R_6 and R_7, which can be the same or different, each are hydrogen, methyl, ethyl or halogen. Especially the compounds wherein n is greater than 0 possess valuable antimycotic properties. Especially good antihypertensive properties have been found in compounds of formula (III) where n is 0 and X is

$$-C=C-$$
(R_{11}, R_{10})

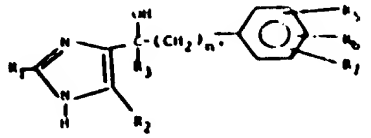
According to the feature of the invention, the compounds of formula (I) wherein R_4 is OH and the compounds of formula (II) are made by a Grignard reaction, in which an imidazolylketone of the formula



wherein R_1, R_2, and R_3 are as defined before, is reacted with an arylalkyl magnesium halide derivative or aryl magnesium halide derivative of the formula:



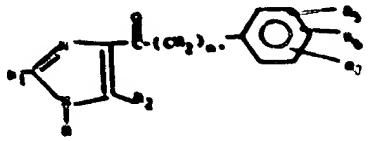
wherein R_5, R_6 and R_7 are as defined before, n' is 0 to 5 and Hal is a halogen atom to give compounds of the formula (III)



wherein R_1, R_2, R_3, R_5, R_6, R_7 and n' are as before.

The arylalkylmagnesium halide derivative can be, for example, an arylalkylmagnesiumbromide derivative, which is prepared by reacting the corresponding arylalkylbromide derivative with magnesium. Suitable solvents for the reaction include a variety of ethers, preferably tetrahydrofuran. The arylalkylmagnesiumhalide derivative is prepared in the usual way by adding the arylalkylmagnesiumhalide derivative in a suitable solvent, e.g. tetrahydrofuran, dropwise onto magnesium turnings covered by tetrahydrofuran, at the boiling point of the reaction mixture. When the magnesium turnings have reacted, the mixture is cooled slightly and the 4-imidazole derivative is added in solid form in small portions or in tetrahydrofurene solution. After the addition, the reaction mixture is refluxed until all of the 4-imidazole derivative has reacted. The reaction time varies between one and five hours.

Another process for the preparation of compounds of formula (III) is a Grignard reaction in which a compound of the formula (IV)

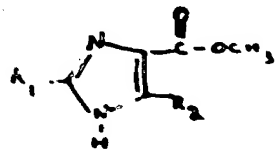


wherein R_1-R_7 and n' are as before, is reacted with a compound of the formula

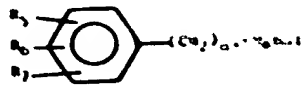
R_3MgHal

wherein R_3 is an alkyl or aryl as defined before and Hal is halogen.

Yet another process for the preparation of compounds of formula (III) is a Grignard reaction in which an imidazole carboxylic acid alkyl ester, preferably the methyl ester of the formula



wherein R_1 and R_2 are as before, is reacted in a first step with a Grignard reagent of the formula



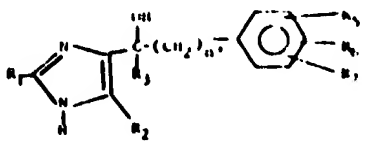
wherein R_5, R_6, R_7 and n' are as before, to give a compound of formula (IV), which in a second step without isolation is reacted with a Grignard reagent of the formula

R_3MgHal

wherein R_3 is as defined before.

Compounds of formula (I) wherein R_4 is H can be prepared by reduction of compounds of formula (II) wherein n' is 0 with hydrogen. A suitable catalyst is e.g. palladium-on-carbon.

Unsaturated compounds of formula (I) wherein R_3 is $=CH_2$, $=CH-CH_3$, $=CH-CH_2CH_3$, $=C(CH_3)-CH_3$ or $=CH-CH_2CH_2CH_3$ or formula (II) wherein R_{10} is hydrogen are prepared by dehydrating compounds of formula (III):



wherein R_1, R_2, R_5, R_6, R_7 are as defined before, R_3 is an alkyl or aryl as defined before and n' is 0 to 5, to give a compound of the formula (V)

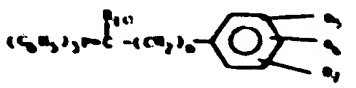
wherein R_1, R_2, R_5, R_6, R_7, and n and n' are as defined before; R_{11} is an alkyl as defined before and R_9 is an alkenyl as defined before.

The dehydration is preferably performed by refluxing in an appropriate acidic solution, e.g. concentrated hydrochloric acid or heating for example with potassiumhydrogen sulfate.

The compounds of formula (V) can further be reduced with hydrogen in the presence of a palladium-on-carbon catalyst to the corresponding saturated compounds of formulae (II) and (III).

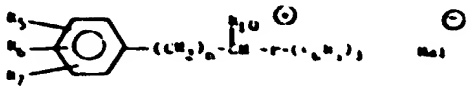
Compounds of formula (II) wherein R_{11} is hydrogen are prepared by a Wittig reaction which comprises reacting an imidazole aldehyde of the formula

wherein R_1 and R_2 are as before, with an aralkylidenetriphenylphosphorane of the formula



wherein R_5, R_6, R_7, R_{10} and n are as defined before, to give the unsaturated compounds of formula (III), which in a further step can be reduced to the corresponding saturated compounds of formula (II) as described above.

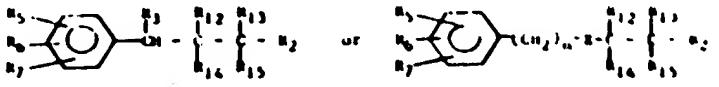
The aralkylidenetriphenylphosphoranes are preferably prepared by reacting the corresponding aralkyltriphenylphosphonium halide of the formula:



wherein R_5, R_6, R_7, R_{10} and n are as before and Hal is halogen, with a basic reagent, preferably butyllithium.

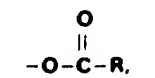
In the Grignard- and Wittig-syntheses described above, the free nitrogen atom in the imidazole starting material can be protected by different methods. Suitable protecting groups are for example benzyl, triphenylsilyl or dialkoxymethane. The removal of the protecting group can be performed in different ways, and depends on the kind of protecting group used. For example, a dialkoxymethane group is removed by acidic hydrolysis and a benzyl group by sodium in liquid ammonia.

The present invention further provides yet another method for preparing compounds of the invention. Thus, according to this embodiment of the invention, a starting material of the formula (VI) or (VII)



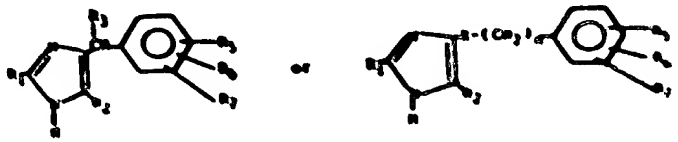
(VI) (VII)

wherein R_2, R_3, R_5, R_6, R_7 and n are as hereinbefore defined; wherein R_{12}, R_{13}, R_{14} and R_{15}, which can be the same or different, are each hydrogen, hydroxy, mercapto, halogen, amino, –O– alkyl of 1 to 7 carbon atoms or



wherein R is an alkyl; or wherein R_{12} and R_{14} can be combined to form a keto group, or R_{13} and R_{15} can be combined to form a keto group, or both R_{12} and R_{14} and R_{13} and R_{15} can simultaneously form keto groups, or

both R_{13} and R_{14} and R_{13} and R_{15} can simultaneously form keto groups; is reacted with a reagent capable of converting said starting material to the corresponding imidazole of the formula



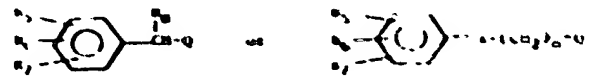
wherein R_1, R_2, R_3, R_4, R_5, R_6, X and n are defined as before. Reagents capable of converting the described starting material to the corresponding imidazole include $NH_3 + CH_2O$ (or a source of ammonia and formaldehyde):

$$HN=C(R_1)-NH_2;\ H-C(=O)-O^-\ NH_4^+;\ HCONH_2;\ R_1-C(=O)-NH_2;\ \text{or } R_1CHO \text{ and } NH_3$$

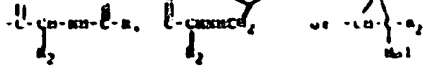
Choice of an appropriate reagent varies with the particular starting material employed.

When R_1 is hydrogen it is preferable to employ formamide as the reagent in cases where, in place of the bromine atom in the aforementioned starting materials, there is instead a hydroxyl, amino or acetyl group. In these instances, formamide is used in excess and acts in part as the solvent. Generally, the reaction is run at the boiling point of formamide for a period of time ranging from one to five hours.

Yet another process for the preparation of the compounds of formula (I) and (II) comprises reacting formamide with a benzene derivative of the formula:

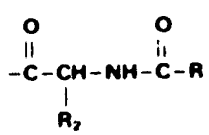


wherein R_3, R_4, R_5, R_6 and n are as defined hereinabove, and Q is a radical of formula

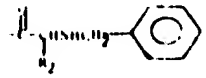


wherein R is a substituted and unsubstituted alkyl, arylalkyl or aryl group, and R_2, Hal and X are as defined hereinabove. Preferably the reaction is performed by vigorously boiling the benzene derivative in formamide, the reaction time varying with the particular material employed.

Reaction times typically are from 30 minutes to 8 hours. Obviously, the formamide treatment will be followed by reaction with an appropriate acid (e.g. HCl) when Q in the starting material is

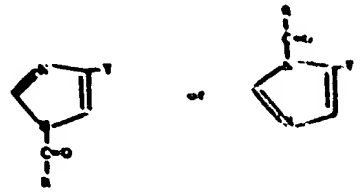


in order to obtain the corresponding compound of formula (I) and (II).

Similarly, when a starting material wherein Q is 

is employed, then the formamide treatment will be followed by hydrogenation, thus affording the desired compound of formula (I) and (II).

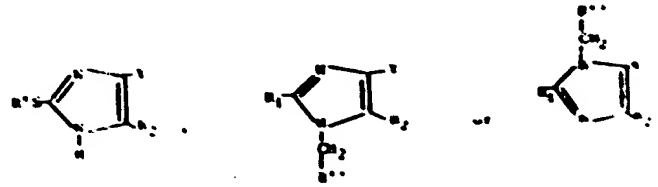
A further process for the preparation of the compounds of the formula (I) and (II) comprises hydrolysing a corresponding N-acetylated compound of the formula (I) and (II)



where Y is the arylalkylresidue determined by the formula (I) and (II), R is an alkyl group of 1 to 7 carbon atoms an aryl radical of 6 to 10 carbon atoms.

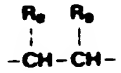
Preferably, the hydrolysis is carried out by boiling the starting material, an N-acylated imidazole derivative, in an aqueous solution of an inorganic acid until the reaction is completed.

Yet another process for the preparation of the compounds of formula (I) and (II) comprises hydrogenating a starting material of the formula



wherein Y is as defined before and R' is an aryl or alkyl and R'' is an aryl group. The hydrogenation is conveniently conducted in the presence of a suitable catalyst and under a hydrogen atmosphere, with stirring or using metallic sodium in liquid ammonia. Suitable catalysts include platinum oxide, palladium-on-carbon and Raney nickel. Reaction temperatures vary with the particular starting material employed, with typical temperatures being 25-70°C.

Yet another method for the preparation of the compounds of formula (I) or (II) wherein X is

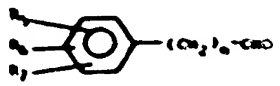


comprises reacting a N-trialkylsilylimidazole of the formula

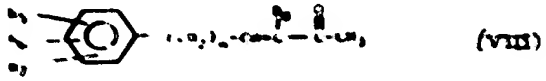
wherein Y is an alkyl group, preferably methyl, with an arylalkylhalogenide of the formulae

wherein R_2, R_5, R_6, R_7, R_8 and R_9 are as before and Hal is a halogen atom, in the presence of a Lewis acid, for example titanium tetrachloride, aluminium chloride or zinc chloride. As solvent can be used for example methylene chloride or chloroform. The reaction is preferably carried out at room temperature stirring the starting materials for 6-12 hours.

The intermediates of formula (VI) and (VII) can be prepared for example as follows
An aldehyde of the formula

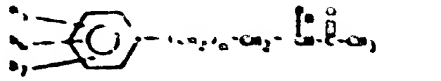


wherein R_5, R_6, R_7 and n are as before, is reacted in alkaline or acidic conditions with a ketone, preferably acetone, to give a compound of the formula (VIII) via direct aldol condensation



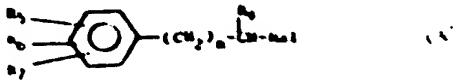
(VIII)

wherein R_8 is an alkyl as defined before.
which compound in a second step is catalytically reduced to give the corresponding saturated compound of the formula:



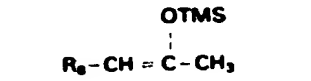
(IX)

which compound in a third step is regioselectively brominated in methanol to give compounds of formula VII.
Another method for the preparation of the compounds of the general formula (VII) is the regioselective alkylation process of ketones in which for example a halide compound of the formula (X)



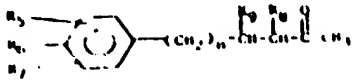
(X)

is reacted with a trimethylsilylenolether derivative of the general formula (XI)



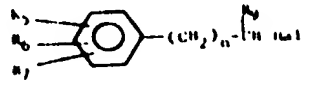
(XI)

wherein R_8 is an alkyl as before, in the presence of a Lewis acid, for example zinc (II) chloride, to give a compound of the formula (XII)



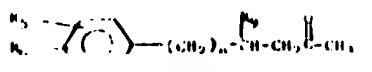
(XII)

The compound of formula (XII) is further brominated as before to give compounds of the formula (VII).
When R_8 and R_2 are hydrogen yet another method for the preparation of compounds of the formula (VII) can be applied. In this method a halide of the general formula (XIII)



(XIII)

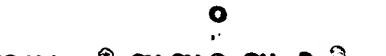
is reacted with lithiated N,N-dimethylhydrazone of acetone followed by hydrolysis to give a compound of the general formula (XIV)



(XIV)

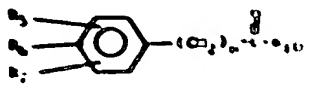
which compounds are brominated as before to give compounds of the formula (VII).

According to another method for the preparation of compounds of the formula (VII), compounds of the formula (VIII) are selectively brominated using as brominating agent for example 2-carboxyethyltriphenylphosphonium perbromide, which has the formula (XV)

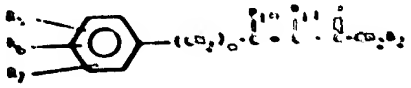


(XV)

Yet another method for the preparation of compounds of the formula (VII) is possible via a directed aldol condensation, in which for example a compound of the formula (XVI)

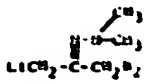


is reacted with the compound (XI) in the presence of a Lewis acid followed by dehydration to give a compound of the formula (XVII)

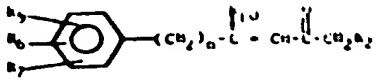


which compound is further brominated as before to give a compound of the formula (VII).

When R_{11} is hydrogen, compounds of the formula (VII) can be prepared from compounds of the formula (XVI), wherein these are reacted with 1-lithiated N,N-dimethylhydrazone of methylalkylketone of the formula (XVIII)



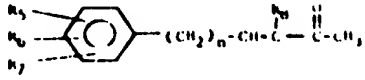
Here in the first step compounds of the formula (XIX) are achieved.



the bromination of which compounds are performed following the method above.

The preparation of compounds of the general formula (VII) can be accomplished from compounds of the general formula (XVII) by hydrogenation of the carbon-carbon bouble bond as well. The bromination in the second step leads to compounds of the formula (VII).

Alkylation of compounds of the general formula (XVII) when R_7 and R_{10} are hydrogen can be accomplished, too. In this method a compound of the formula (XX)



is reacted with an alkylation reagent such as dialkyllithiocuprate (XXI) which undergoes 1,4-conjugate addition

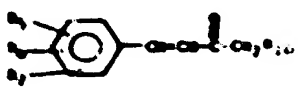
$(R)_2CuLi$ (XXI)

to form compounds of the formula (XII).

Condensation of an arylalkylketone or its vinylogue with 4-imidazole aldehydes of the formula (XXII).

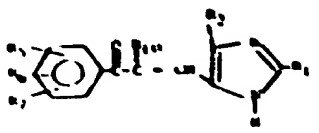
provides further another method for the preparation of compounds according this invention. The condensation is performed for example in aqueous alcohol catalysed by sodium hydroxide. Arylalkylketones or their vinylogues have the general formulae (XXIII) and (XXIV)

(XXIII)

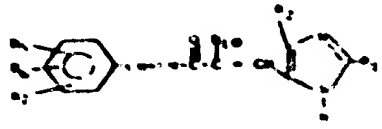


(XXIV)

In the first step this condensation gives unsaturated ketones of the formulae (XXV) and (XXVI)

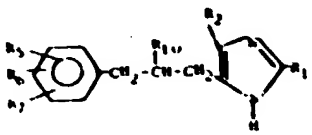


(XXV)

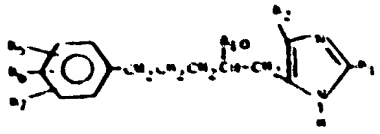


(XXVI)

which compounds are then hydrogenated to the end products according to the formulae (XXVII) and (XXVIII)



(XXVII)



(XXVIII)

As stated herein above, the compounds of the general formula (I) and (II) and their non-toxic, pharmaceutically acceptable acid addition salts have valuable pharmacological properties and have been found to possess excellent antihypertensive properties.

Tests have shown that they also possess other pharmacological properties as well, for example, antithrombotic activity. Furthermore, antimycotic and antifungal properties have been found, too.

The processes described above for the preparation of compounds of formula (II) wherein X is

result mainly in the trans isomer of the compound. The trans isomer can be converted to the cis isomer according to known methods, e.g. by heating it in the presence of an acid or by irradiating it with ultraviolet light.

Administration of isomeric compounds of formula (I) and (II), their non-toxic, pharmaceutically acceptable acid salts or mixtures thereof may be achieved parenterally, intravenously or orally. Typically, an effective amount of the derivative is combined with a suitable pharmaceutical carrier. As used herein, the term "effective amount" encompasses those amounts which yield the desired activity without causing adverse side-effects. The precise amount employed in a particular situation is dependent upon numerous factors such as method of administration, type of mammal, condition for which the derivative is administered, etc., and of course the structure of the derivative.

The pharmaceutical carriers which are typically employed with the derivatives of the present invention may be solid or liquid and are generally selected with the planned manner of administration in mind. Thus, for example, solid carriers include lactose, sucrose, gelatin and agar, while liquid carriers include water, syrup, peanut oil and olive oil. Other suitable carriers are well-known to those skilled in the art of

determined by the following procedure. Sprague-Dawley rats of normal weight were first anesthetized with urethane. After this, the femoral artery was connected by way of a polyethylene tube with a blood pressure transducer. The test substance was then injected into the femoral vein and the blood pressure and the pulse frequency were registered with a recorder.

In a further test for anti-hypertensive properties unanesthetized Wistar spontaneous hypertensive rats (SHR) were used. The test derivative was administered perorally by way of a tube into the stomach. The blood pressure was measured from the tail using an indirect bloodless method.

In another experiment 3 months old spontaneous hypertensive male rats were used to test the anti-hypertensive properties during a period of 4 weeks. The test derivative was administered daily to each rat in the drinking water and the blood pressure of the tail was measured by a standard electric method.

The antithrombotic activity was investigated in vitro. The inhibiting activity of the compounds against ADP- and collagen-induced aggregation of thrombocytes was measured. In the test thrombocytes from a cow was used. To 1.2 ml of plasma containing 250000 thrombocytes/mm^3 were added 50µl of a solution of the compound to be tested. After 10 min incubation either ADP or collagen was added. The aggregation of the thrombocytes was turbidimetrically determined at λ = 605 n m.

The antimicrobial activity was determined *in vitro* according to a qualitative test for antibacterial and antifungal activity, using the agar diffusion method, against the following standard organisms: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Proteus mirabilis*, *Pseudomonas aeruginosus*, *Candida albicans* and *Aspergillus niger*.

The antifungal activity was determined *in vitro* against the following fungi: *Trichophyton rubrum*, *Trichophyton mentagrophytis*, *Microsporum canis*, *Epidermophyton floccosum*, *Chrysosporum*, *Candida albicans*, *Candida guilliermondi* and *Saccaromyces cerevisiae*. The fungi were cultured by plating on an agar nutrient medium. The compound to be tested was added before the incubation. A measure of the efficiency of the compound tested is the radius of the circle, within which the growth of the fungi has been inhibited.

Acute toxicity was determined by using female mice of NMRI-Strain with an age of about 7 months and weighing 30-40 g. The administration of the test compound was i.v.

Thus, the compound 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole, which has a LD_{50} value greater than 30 mg/kg i.v., was found in the blood pressure study with anesthetized rats of normal weight described above to cause a registrable lowering of the blood pressure at a dose of 3 µg/kg i.v. At a dose of 10 µg/kg i.v. the blood pressure lowering was quite clear and at a dose of 100-300 µg/kg i.v. the reduction of the blood pressure was on an average 38 %. The duration of the effect was at least 30 minutes (after which time the determination was interrupted).

The compound 4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole caused a blood pressure lowering of 20 per cent measured 30 minutes after the administration at a dose of 100 µg/kg.

The compound 4-[(α-methyl)-(2,6-dimethylbenzyl]imidazole caused a blood pressure lowering of 50 % at a dose of 30-100 µg/kg.

The compound 4-[(α-methyl)-2,3-dimethylbenzyl] imidazole caused a blood pressure drop of 55% at 10 mg/kg.

In the Examples below, where ^{1}H-NMR spectrum shifts are presented, the NMR spectra were determined with a Perkin-Elmer R 24 or a Bruker WP80DS apparatus using an external tetramethylsilane standard, from which the presented chemical shifts (δ, ppm) are tabulated. The letters s, d, t and m are used to indicate a singlet, doublet, triplet or multiplet, respectively and coupling constants in hertz when given. In the same connection, the number of hydrogen atoms is also stated. The compounds which are indicated as bases are tested in deuterium methanol, deuterium acetone or deuterium chloroform, while the values for compounds which are indicated as hydrochlorides were determined in deuterium oxide. The presented ^{13}C-NMR-spectrum were determined with a Bruker WP80DS apparatus.

The mass-spectra were determined with a Perkin-Elmer RMU-6E apparatus using direct inlet system. The temperature employed was the lowest temperature needed for the evaporation of the compound as base. In the examples the strongest and the most essential fragment-ions from a structural viewpoint are given as m/e values. In parenthesis is given the intensity of the fragment-ion in relation to the main peak.

EXAMPLE 1

4-[(α,α-bis(2-methylphenyl)hydroxymethyl]-5-methylimidazole

4.9 g (0.2 mol) of dry magnesium turnings are covered with 50 ml of dry tetrahydrofuran. The mixture is heated to boiling and a solution of 34 g (0.2 mol) of 2-bromotoluene in 50 ml dry tetrahydrofuran is added dropwise at such a rate that a smooth reaction is maintained. After the addition is complete, the reaction mixture is refluxed for about 30 minutes until the magnesium turnings no longer react. The reaction mixture is then cooled to about 50°C and 9.3 g of 5-methyl-4-imidazole carboxylic acid methyl ester are added in small portions. After the addition is complete, the mixture is refluxed for another 2 hours and the solvent is then distilled off to give about half of the original volume. The mixture is cooled and poured into 300 ml of cold water containing 15 ml of concentrated sulfuric acid, with agitation. The stirring is continued for an additional 15 minutes and the mixture is then filtered. The precipitate, filtered from the acidic water, which is

MS: 292 (55 %), 274 (69 %), 259 (100 %), 232 (7 %), 217 (9 %), 201 (52 %), 199 (72 %), 167 (18 %), 139 (63 %)

EXAMPLE 2

4-[α,α-bis(2-methylphenyl)hydroxymethyl]imidazole

A Grignard reagent is prepared from 68.4 g of o-bromotoluene and 9.6 g of Mg-turnings in 200 ml of THF. To this solution 12.6 g of 4-imidazole carboxylic acid methylester are added at 50°C and the reaction mixture is refluxed for 5 hours.

The mixture is then poured into cold water, which includes 60 ml of conc. HCl. The hydrochloride of the product is filtered off, washed with chloroform and recrystallized from isopropanol, yield 23 g (73 %), m.p. 178-179°C. Liberation of hydrochloride is achieved in water-ethanol with sodiumhydroxide, m.p. 138-140°C.

^{1}H-NMR (HCl-salt): 1.9 (s, 6H), 4.6 (s, 3H), 6.7 (s, 1H), 7.0 (s, 8H), 8.7 (s, 1H)

EXAMPLE 3

4-(α,α-diphenyl)hydroxymethyl-5-methylimidazole

The compound is prepared by the method described in Example 2 except that bromobenzene is used in place of o-bromotoluene and 5-methyl-4-imidazole carboxylic acid methyl ester in place of 4 imidazolecarboxylic acid methyl ester; yield 18.5 g (70%), m.p. 188-190°C (as base from ethanol)

^{1}H-NMR: 1.4 (s, 3H), 4.7 (s, 2H), 7.0 (s, 10H), 7.2 (s, 1H)

MS: 264 (80 %), 246 (78 %), 231 (28 %), 218 (20 %), 204 (9 %), 187 (100 %), 109 (64 %), 105 (26 %), 77 (34 %)

EXAMPLE 4

4-[(α-(2-methylphenyl)]-2-methylbenzyl]imidazole

The starting material, 4-[α, α-bis(2-methylphenyl)hydroxymethyl]-imidazole is dissolved in 100 ml of acetic acid. 100 mg of Pd/C are added and the reaction mixture is stirred vigorously in a hydrogen atmosphere at about 60°C until the reaction is completed. The mixture is then filtered and distilled to a smaller volume. 70 ml of water are added and that mixture is then washed twice with 20 ml portions of chloroform. The aqueous phase is made alkaline with NaOH and extracted with chloroform (3 × 40 ml). The combined chloroform extracts are washed with water (1 × 10 ml) and dried over Na_2SO_4. The solution is evaporated to dryness. Yield 93 %, m.p. 228-231°C (from ethanol). Hydrochloride from ethyl acetate-isopropanol m.p. 245-254°C

^{1}H-NMR: 2.1 (s, 6H), 4.7 (s, 2H), 5.8 (s, 1H), 6.6 (s, 1H), 6.9 (m, 8H), 8.7 (s, 1H)

EXAMPLE 5

4-(α-phenylbenzyl)-5-methylimidazole

The compound is prepared by reduction of 4-(α,α-diphenyl)hydroxymethyl-5 methylimidazole using a palladium-on-carbon catalyst as described in Example 4.

EXAMPLE 6

4-(α-phenylbenzyl)-5-methylimidazole

The compound is prepared from 4-(α, α-diphenyl)hydroxymethyl-5-methylimidazole according to the method in Example 4. Yield 69 %, m.p. 198-204°C (from ethanol).

^{1}H-NMR: 1.6 (s, 3H), 4.5 (s, 1H), 5.3 (s, 1H) 6.8 (s, 10H), 7.3 (s, 1H)

EXAMPLE 7

4-[(α-(2-methylphenyl)-α-(2-methylbenzyl)]-5-methylimidazole

The compound is prepared according to the method in Example 4 using 4-[α,α-bis-(2-methylphenyl)hydroxymethyl]-5-methylimidazole as starting material. Yield 79%, m.p. 178-180°C (from water-ethanol).

^{1}H-NMR: 1.4 (s, 3H), 1.8 (s, 6H), 4.6 (s, 1H), 5.35 (s, 1H), 7.1 (m, 8H), 7.15 (s, 1H)

EXAMPLE 8

4-[(α-(2,3-dimethylphenyl)-α-methyl]hydroxymethyl]imidazole, 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)ethylene and 4-(α-methyl-2,3-dimethylbenzyl)imidazole

For the preparation of 2,3-dimethylmagnesiumbromide in the first step, 4.9 g of dry magnesium turnings are covered with 50 ml of dry tetrahydrofuran.

The mixture is heated to boiling and a solution of 37 g of 2.3-dimethylbromobenzene in 50 ml dry of tetrahydrofuran is added dropwise at such a rate that a smooth reaction is maintained. After the addition is complete the reaction mixture is refluxed for about 30 minutes until the magnesium turnings no longer react.

In the same way in another flask of methylmagnesiumbromide is prepared from 2.4 g of magnesium turnings and 9.6 g of methylbromide in tetrahydrofuran.

Yet another flask of 12.6 g of 4-imidazolecarboxylic acid methylester, is added to 100 ml of dry tetrahydrofuran and the mixture is stirred while heating to about 50°C. To this is then dropped the earlier

water containing 50 ml of concentrated sulfuric acid, with agitation. The stirring is continued for an additional 15 minutes and the mixture is then filtered.

The pH of the filtrate is adjusted slightly basic and the mixture is extracted three times with 50 ml portions of methylene chloride. The combined methylene chloride extracts are washed with water and evaporated to dryness. The residue which contains crude 4-[(α-(2,3-dimethylphenyl)-α-methyl]hydroxymethyl imidazole is further purified column chromatographically in silicagel using chloroform methanol as eluent. 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)-ethylene is then obtained from the above product by heating it with potassiumhydrogen sulphate at 136°C.

^{1}H-NMR (HCl-salt): 2.104 (s, 3H), 2.313 (s, 3H), 5.187 (s, 2H), 5.358 (s, 1H), 6.108 (s, 1H), 7.03-7.22 (m, 4H), 8.98 (s, 1H)

^{13}C-NMR (HCl-salt): Signals at ppm: 18.073, 21.857, 118.789, 119.456, 127.961, 129.475, 132.238, 135.802, 136.498, 136.892, 137.921, 139.949, 140.070

Melting point as base: 137-140°C

4-(α-methyl-2,3-diemthylbenzyl)imidazole is obtained via hydrogenation with palladium-on-carbon catalyst in 2-N HCl according to the method described before.

^{1}H-NMR (HCl-salt): 1.708 (d, 3H), 2.370 (broad s, 3H), 4.688 (q, 1H), 4.933 (s, 2H), 7.079-7.263 (m, 3H), 7.361 (s, 1H), 8.780 (s, 1H)

^{13}C-NMR (HCl-salt): Signals at ppm: 16.529, 21.917, 22.462, 34.662, 117.881, 126.680, 128.385, 131.679, 135.650, 136.952, 140.161, 140.163, 142.855

By the same method for example the following compounds were prepared:
4-(α-methyl-2,6-dimethylbenzyl)imidazole
4-(α-ethyl-2,3-dimethylbenzyl)imidazole
4-(α-butyl-2-methylbenzyl)imidazole
4-(α-methyl-2,3-dimethylbenzyl)-2-methylimidazole

EXAMPLE 9

4-(2,6-dimethylphenyl)-3-buten-2-one

13.4 g (0.1 mol) of 2,6-dimethylbenzaldehyde, 100 ml of acetone, 100 ml of water and 2 g of calcium hydroxide are mixed together and refluxed for about 20-25 h with agitation. The precipitate is filtered off from the cold reaction mixture. 1 l of ice water is added to the filtrate with agitation. The product is crystallized at a yield of about 90 %. M.p. of the recrystallized product: 34-35°C.

^{1}H-NMR: 7.55 (1Hd, 16.5), 7.00 (3Hs), 6.26 (1Hd, 16.5), 2.37 (3Hs), 2.31 (6Hs)

EXAMPLE 10

4-(2,6-dimethylphenyl)-2-pentanone

To a mixture containing 20 g of CuI and 50 ml of tetrahydrofuran (THF) are added 105 ml of methyllithium dropwise during with agitation in a nitrogen atmosphere at a temperature of 0°C or lower until the yellow precipitate barely dissolves. Then 8.7 g of 4-(2,6-dimethylphenyl)-3-buten-2-one in 50 ml of THF are added slowly at 0°C. The stirring is continued for an additional 2 h with a gradual increase of the temperature to + 25°C. The reaction mixture obtained is hydrolysed with 300 ml of a solution of NH_4Cl. The ether is removed, dried and evaporated to give the crude product.

^{1}H-NMR: 6.85 (3Hs), 3.78 (1Hq + t, 7.5), 2.76 (2Hd, 7.5), 2.34 (6Hs), 1.99 (3Hs), 1.27 (3Hd, 7.5)

According to the same method, the compound 4-phenyl-2-pentanone was prepared.

^{1}H-NMR: 7.10 (5Hs), 3.26 (1Hq+t, 7.5), 2.62 (2Hd, fine structur), 1.94 (3Hs), 1.20 (3Hd, 7)

Similarly 4-(3,4-dimethylenedioxyphenyl)-2-pentanone

^{1}H-NMR: 6.62 (3H, s), 5.83 (2H, s), 3.20 (1Hq + t, 7), 2.67 (2H, d7), 2.04 (3Hs), 1.26 (3Hd7)

EXAMPLE 11

1-bromo-4-(2,6-dimethylphenyl)-2-pentanone

To 3.8 g of 4-(2,6-dimethylphenyl)-2-pentanone in 25 ml of dry methanol 1.04 ml of bromine are added dropwise rapidly at a temperature not higher than + 5°C. Stirring is continued until the bromine colour disappears, while the temperature slowly rises to + 20°C. After evaporation the product is obtained at a yield of at least 70 %.

^{1}H-NMR: 6.98 (3Hs), 3.80 (1Hm), 3.67 (2Hs), 3.02 (2Hd), 2.35 (6Hs), 1.33 (3Hd, 7)

According to the same method the compounds 1-bromo-4-phenyl-2-pentanone and 1-bromo-4-(2,6-dimethylphenyl)-3-methyl-2-butanone were prepared.

Similarly using two equivalents of bromine:
1-bromo-4-(2-bromo-4,5-methylenedioxyphenyl)-2-pentanone

^{1}H-NMR: 6.9 (1H, s), 6.67 (1H, s), 5.87 (2Hs), 3.80 (2Hs), 2.9 (3Hm), 1.19 (3Hd7)

EXAMPLE 12

4-[2-(2,6-dimethylphenyl)propyl]imidazole

This is dissolved in ethyl acetate and HCl/ethylacetate is added. The product is evaporated to dryness, washed with ether, dissolved in water, neutralized with $NaHCO_3$ and extracted with methylene chloride. The evaporation residue is dissolved in ethyl acetate and the final product is precipitated as oxalate or hydrochloride. M.p. of the hydrochloride 194-198°C.
^{1}H-NMR (HCl-salt): 8.70 (1Hs), 6.9 (4Hs), 3.65 (1Hm), 3.21 (2H, d 8) 2.39 (8H broad s), 1.48 (3Hd 7)

According to the same method, the following compounds were prepared:
4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole. M.p. of the oxalate 161-6°C.
^{1}H-NMR (oxalate): 9.75 (1H broad s), 7.05 (1Hs), 7.00 (3Hs), 3.0 (3Hm), 2.20 (6Hs), 1.31 (3Hd)
4-(2-phenylpropyl)imidazole (as oxalate)
^{1}H-NMR: 8.52 (1Hs), 7.22 (5Hs), 6.97 (1Hs), 3.05 (3Hm), 1.35 (3Hd)
M.p of the oxalate: 166-168°C.
4-[2-(3,4-methylenedioxyphenyl)propyl]imidazole
^{1}H-NMR (as oxalate): 8.70 (1H, s), 7.11 (1H, s), 6.78 (3H, m), 5.95 (2H, s), 3.08 (3H, m), 1.40 (3H, d)
M.p. of oxalate: 154-156°C.
4-[2-(2,6-dimethylphenyl)butyl]imidazole
M.p. of oxalate 176-9°C.
^{1}H-NMR: 8.25 (1H, broad s), 6.95 (3H, s), 6.68 (1H, s), 3.2 (3H, m), 2.45 (3H, s), 2.6-2.0 (2H, m), 2.06 (3H, s), 1.87 (3H, t)
4-[2-(2-bromo-4,5-methylenedioxyphenyl)propyl]imidazole

EXAMPLE 13

4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one

A mixture of 13.4 g of 2,6-dimethylbenzaldehyde and 15 ml of 2-butanone is saturated with gaseous HCl with stirring. The starting temperature is 0°C, and it is raised to 20-25°C in 2 h. The reaction mixture is poured into 0.5 l of cold water, extracted with toluene and washed with a $NaHCO_3$-solution. The dried toluene extract is filtered, toluene and free 2-butanone are distilled off. The product is obtained by crystallization from di-isopropylether. M.p. 43-44°C.
^{1}H-NMR: 7.38 (1Hs), 6.98 (3Hs), 2.42 (3Hs), 2.11 (6Hs), 1.59 (3Hd, 1.4)

EXAMPLE 14

1-bromo-4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one

To a mixture of 3.8 g of 4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one in 50 ml of THF a solution of 13 g of 2-carboxyethyltriphenylphosphoniumperbromide in 50 ml of THF is added dropwise at room temperature. Stirring is continued for another 2 h. 200 ml of water and 100 ml of ligroin are added. The organic layer is washed with a Na_2CO_3-solution and water. After filtration and evaporation 5.5 g of crude product containing 85-90 % of 1-bromo-4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one are obtained.
^{1}H-NMR: 7.51 (1H broad s), 7.05 (3Hs), 4.27 (2Hs), 2.18 (6Hs), 1.68 (3Hd, 1.3)

EXAMPLE 15

4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole E-isomer

The compound is prepared according to the method described in Example 12, except that 1-bromo-4-(2,6-dimethylphenyl)-3-methyl-3-buten-2-one is used instead of 1-bromo-4-(2,6-dimethylphenyl)-2-pentanone.
M.p. of the hydrochloride 260-262°C.
^{1}H-NMR: 8.82 (1H, d), 7.36 (1H, d), 7.20 (1H, broad s), 7.08 (3Hs), 2.20 (6Hs), 1.82 (3H,d,1.2)

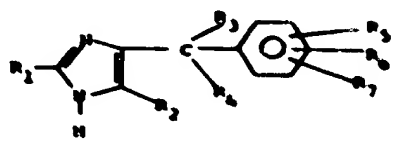
EXAMPLE 16

4-[(α-methyl)-2,6-dimethylbenzyl]imidazole

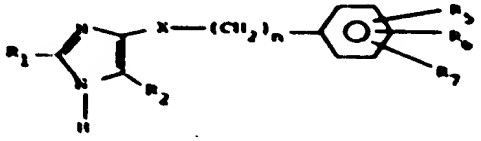
To a mixture of N-(trimethylsilyl)imidazole (1.4 g) and titanium tetrachloride (1.6 ml) in dry chloroform (20 ml) a solution of 1-chloro-1-(2,6-dimethylphenyl)ethane (1.7 g) in dry chloroform (10 ml) was added. After stirring for 5 h at room temperature the product mixture was poured onto water, washed with ether and neutralized with sodium hydrogen carbonate. Filtration and extraction with methylene chloride gave 4-[(α-methyl)-2,6-dimethylbenzyl]imidazole, yield 33 %.
^{1}H-NMR; δCDCl$_3$ 11.4 (1H, broad), 7.19 (1H, s), 6.83 (3H, s), 6.56 (1H, s), 4.52 (2H, q 6), 2.11 (6H, s), 1.63 (3H,d 6)
M.p. of the hydrochloride: 208-10°C.
^{13}C-NMR (as hydrochloride): δ CD$_3$OD 139.8 (1C, s), 139.1 (1C, s), 137.6 (2C, s), 134.9 (1C, d), 130.8 (2C, d), 128.4 (1C, d), 116.6 (1C, d), 32.8 (1C, d), 20.8(2C, q), 17.0 (1C, q)

CLAIMS

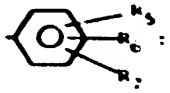
1. Substituted imidazoles of the general formula



or



wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or $-CH_2OH$; R_2 is H or CH_3; R_3 is $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$, $-CH_2CH=CH_2$, or



and R_4 is H or OH; or R_3 and R_4 together represent

$=CH_2$, $=CH-CH_3$, $=CH-CH_2-CH_3$, $=C(CH_3)-CH_3$, or $=CH-CH_2CH_2CH_3$;

X is $-CH(R_8)-CH(R_9)-$ or $-C(R_{11})=C(R_{10})-$; R_5, R_6 and R_7, which can be the same or different, are H, $-CH_3$, $-CH_2CH_3$, halogen, OH or $-OCH_3$ or R_5 is hydrogen and R_6 and R_7 together form an $-O-CH_2-O-$ bridge between two adjacent carbon atoms in the phenyl group; $-CHR_8-$ is $-CH_2-$, $-CH(CH_3)-$, $-CH(CH_3)-$, $-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(CH(-CH(CH_3)-CH_3)-$, $-CH(-CH_2CH_2CH_2CH_3)-$, or

$C=CH_2$, $C=CH-CH_3$, $C=CH-CH_2CH_3$, $C=C(CH_3)-CH_3$, or

$C=CH-CH_2CH_2CH_3$; R_9 is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$ or OH; R_{10} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$, or $-CH_2CH_2CH_2CH_3$; R_{11} is H, $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$; n is 0 to 4; provided that

- when R_4 is OH, R_1 is H or CH_3 and R_3 is  ;

- when R_1, R_2 and R_6 all are hydrogen and R_3 is  :

then R_5, R_6, R_7 are not all simultaneously hydrogen,
- R_8 and R_9 are not simultaneously hydrogen, and
- R_{11} and R_{10} are not simultaneously hydrogen;

and their non-toxic pharmaceutically acceptable acid addition salts.

2. A compound of formula (I) or (II) according to Claim 1 wherein each of R_5, R_6 and R_7, which can be the same or different, is hydrogen, methyl, ethyl or halogen.

3. A compound of formula (I) according to Claim 1 or 2 wherein R_4 is hydrogen and R_3 is methyl, ethyl, propyl, isopropyl or butyl.

4. A compound of formula (I) according to Claim 3 wherein R_1 is methyl.

5. A compound of formula (II) according to Claim 1 or 2 wherein X is

$$-\overset{R_{11}}{C} = \overset{R_{10}}{C}-$$

and R_{10} is hydrogen.

6. A compound of formula (II) according to Claim 1 or 2 wherein X is

$$-\overset{R_{11}}{C}=\overset{R_{10}}{C}-$$

and R_{11} is hydrogen.

7. A compound of formula (II) according to Claim 1 or 2 wherein X is

$$-\overset{R_8}{CH}-\overset{R_9}{CH}-$$

and R_9 is hydrogen.

8. A compound of formula (II) according to Claim 1 or 2 wherein X is

$$-\overset{R_8}{CH}-\overset{R_9}{CH}-$$

and R_8 is hydrogen.

9. A compound of formula (II) according to any of claims 1, 2 and 5-8 wherein R_1 is hydrogen or methyl.

10. A compound of formula (II) according to any of claims 1, 2 and 5-9 wherein n is 0 or 1.

11. A compound of formula (II) according to Claim 1 wherein each of R_5, R_6 and R_7, which can be the same of different, is hydrogen, methyl, ethyl or halogen; R_1 is hydrogen or methyl; R_2 is hydrogen or methyl, R_8 or R_{11} is methyl, ethyl or isopropyl, R_9 or R_{10} is hydrogen, and n is 0.

12. 4-[α,α-bis(2-methylphenyl)hydroxymethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

13. 4-[[α-(2-methylphenyl)]-2-methylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

14. 4-(α-phenylbenzyl)-5-methylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

15. 4-[[α-(2,6-dimethylphenyl)]-α-methyl]hydroxymethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

16. 4-[[α-(2,3-dimethylphenyl)]-α-methyl]hydroxymethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

17. 4-[α,α-bis(2-methylphenyl)hydroxymethyl]-5-methylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

18. 4-[[α-(2-methylphenyl]-2-methylbenzyl-5-methylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

19. 4-[(α-methyl)-2,6-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

20. 4-[(α-methyl)-2,3-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid

22. 4-[(α-butyl)-2,3-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
23. 4-[(α-methyl)-2,3-dimethylbenzyl]-2-methylimidazole and its nontoxic pharmaceutically acceptable acid addition salts.
24. 4-[(α-propyl)-2-methylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
25. 4-(α-methyl)-2-methylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
26. 4-[(α-methyl)-2,5-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
27. 4-[α-ethyl-α-(3-methylphenyl)-hydroxymethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
28. 4-[α-butyl-α-(2,3-dimethylphenyl)-hydroxymethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
29. 4-[α-methyl-α-(2,3-dimethylphenyl)-hydroxymethyl]-2-methylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.
30. 4-[α-propyl-α-(2-methylphenyl)-hydroxymethyl]imidazole and its non toxic pharmaceutically acceptable acid addition salts.
31. 4-[α-methyl-α-(2-methylphenyl)-hydroxymethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
32. 4-[α-methyl-α-(2,5-dimethylphenyl)-hydroxymethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
33. 4-[2-(2,6-dimethylphenyl)-1-methylethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
34. 4-[2-(2,6-dimethylphenyl)propyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
35. 4-[2-(2,6-dimethylphenyl)-1-methylpropyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
36. 4-[2-(2,6-dimethylphenyl)-2-hydroxyethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
37. 4-(2-phenylpropyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
38. 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
39. 4-[2-(2,6-dimethylphenyl)-1-propenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
40. 4-(2-methyl-4-phenyl-1-butenyl)imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
41. 4-[2-(4-chlorophenyl)-1-methylpropyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
42. 4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
43. 4-[3-(2,6-dimethylphenyl)-2-methyl-1-propenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
44. 4-[2-(2,6-dimethylphenyl)-1-ethylethenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
45. 4-[α, α-bis-(2,3-dimethylphenyl)hydroxymethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
46. 4-[α-(2,3-dimethylphenyl)-2,3-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
47. 4-[(α-ethyl)-2,6-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
48. 4-[(α-ethyl)-2,3-dimethylbenzyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
49. 4-[2-(2,3-dimethylphenyl)-1-methylethenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
50. 4-[2-(2,6-dimethylphenyl)-1-isopropylethenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.
51. 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-2-methylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.
52. 4-[2-(2,6-dimethylphenyl)-1-methylethenyl]-5-methylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.
53. 4-[2-(2,6-dichlorophenyl)-1-methylethenyl]imidazole and its non-toxic pharmaceutically acceptable

55. 4-[3-(2,6-dimethylphenyl)-1-oxyl-1-propenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

56. 4-[5-(2,6-dimethylphenyl)-1-methyl-1-pentenyl]-5-methylimidazole and its non-toxic pharmaceutically acceptable acid addition salts.

57. 4-[5-(2,6-dimethylphenyl)-1-methylpentyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

58. 4-[4-(2,6-dichlorophenyl)-1-methyl-1-butenyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

59. 4-[2-(2,6-dimethylphenyl)-1-ethylethyl]imidazole and its non-toxic pharmaceutically acid addition salts.

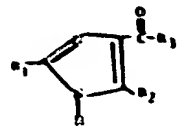
60. 4-[2-(2,6-dimethylphenyl)-2-ethylethyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

61. 4-[2-(3,4-methylenedioxyphenyl)propyl]imidazole and its non-toxic pharmaceutically acceptable acid addition salts.

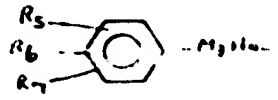
62. 1-(4-imidazolyl)-1-(2,3-dimethylphenyl)-ethylene and its non-toxic pharmaceutically acceptable acid addition salts.

63. 1-(4-imidazolyl)-1-(2,6-dimethylphenyl)-ethylene and its non-toxic pharmaceutically acceptable acid addition salts.

64. A process for the preparation of a compound of formula (I) as claimed in Claim 1, wherein R_6 is OH, which comprises reacting an imidazolylketone of the formula

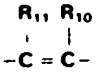


wherein R_1 and R_2 are as defined in Claim 1 and R_3 is as an alkyl or aryl as defined in claim 1 with an aryl magnesium halide derivative of the formula

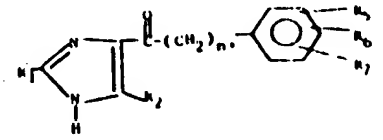


wherein R_5, R_6, R_7 are as defined in claim 1 and Hal is halogen.

65. A process for the preparation of a compound of formula (I) or (III) as claimed in Claim 1, wherein X is



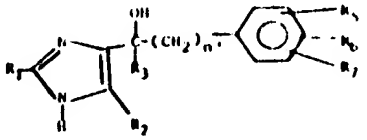
and R_{10} is hydrogen, which comprises reacting a compound of the formula



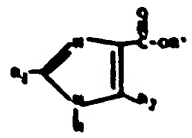
wherein R_1-R_7 are as defined in claim 1 and n' is 0 to 5 with a compound of the formula

R_3MgHal

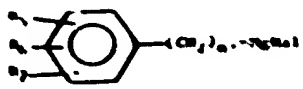
wherein R_3 is an alkyl or an aryl as defined in Claim 1 and Hal is halogen, to give a compound of the formula



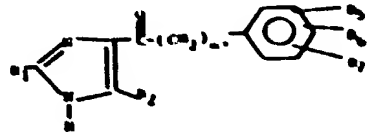
66. A process for the preparation of a compound of formula (I) or (II) as claimed in Claim 1, which comprises reacting an imidazole carboxylic acid alkyl ester of the formula



wherein R_1 and R_2 are as defined in claim 1 and R' is alkyl in a first step with a Grignard reagent of the formula



wherein R_5, R_6, R_7 are as defined in claim 1 and n' is 0 to 5, to give a compound of the formula

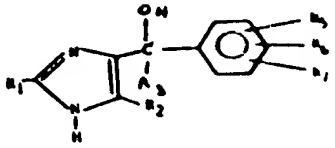


which in a second step is reacted with a Grignard reagent of the formula

R_3M_gHal

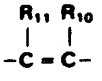
wherein R_3 is an alkyl or aryl as defined in Claim 1, to give a product, which in the final step is dehydrated to give a compound of formula (I) or (II).

67. A process for the preparation of a compound of formula (I) as claimed in Claim 1 wherein R_4 is hydrogen, which comprises catalytic reduction of a compound of the formula

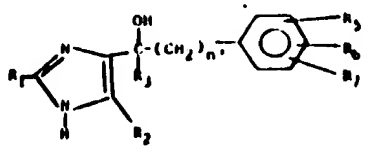


wherein R_1, R_2, R_5, R_6 and R_7 are as defined in Claim 1 and R_3 is an alkyl or aryl as defined in Claim 1.

68. A process for the preparation of a compound of formula (II) as claimed in Claim 1 wherein X is



and R_{10} is hydrogen, which comprises dehydration of a compound of the formula

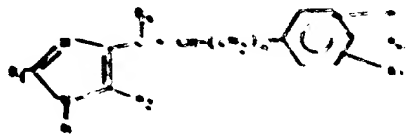


wherein R_1, R_2, R_5, R_6, R_7 are as defined in Claim 1, R_3 is an alkyl or aryl as defined in Claim 1 and n' is 1 to 5.

69. A process for the preparation of a compound of formula (II) as claimed in Claim 1 wherein X is

$$-CH-CH-$$
$$R_8 \quad R_9$$

and R_9 is hydrogen, which comprises catalytic reduction of a compound of the formula



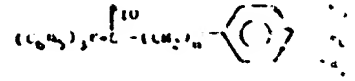
wherein R_1, R_2, R_3, R_4, R_7 and n are as defined in Claim 1 and R_8 is alkyl as in Claim 1.

70. A process for the preparation of a compound of formula (II) as claimed in Claim 1 wherein X is

$$-C=C-$$
$$R_{11}\ R_{10}$$

and R_{11} is hydrogen, which comprises reacting an imidazole aldehyde of the formula

wherein R_1 and R_2 are as defined in claim 1, with an aralkylidenetriphenylphosphorane of the formula



wherein R_5, R_6, R_7, R_{10} and n are as defined in Claim 1.

71. A process for the preparation of a compound of formula (I) or (II) as claimed in Claim 1, wherein X is

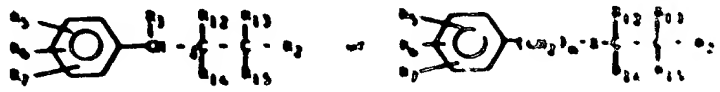
$$-CH-CH-$$
$$R_8 \quad R_9$$

which comprises reacting a N-trialkylsilylimidazole of the formula

wherein Y is an alkyl group, preferably methyl, with an arylalkylhalogenide of the formula

wherein R_3, R_5, R_6, R_7, R_8 and R_9 are as defined in claim 1 and Hal is a halogen atom, in the presence of of a Lewis acid.

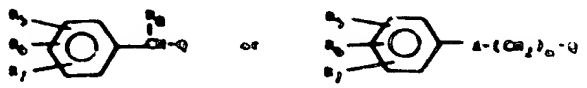
72. A process for the preparation of a compound as claimed in Claim 1, which comprises reacting a starting material of the formula



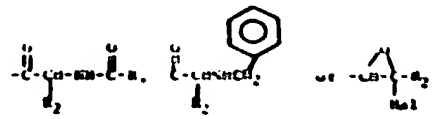
wherein R_1, R_2, R_3, R_6, R_7 and n are as defined in claim 1 and R_{12}, R_{13}, R_{14} and R_{15}, which can be the same or different, are each hydrogen, hydroxy, mercapto, halogen, amino, -O- alkyl of 1 to 7 carbon atoms or

wherein R is an alkyl; or wherein R_{12} and R_{14} can be combined to form a keto group, or R_{13} and R_{15} can be combined to form a keto group, or both R_{12} and R_{14} and R_{13} and R_{15} can simultaneously form keto groups, with a reagent capable of converting said starting material to the corresponding imidazole.

73. A process for the preparation of a compound as claimed in Claim 1 which comprises reacting formamide with a compound of the formula

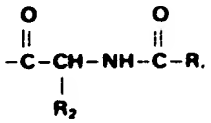


wherein R_5, R_6, R_7, R_8 and n are as defined in Claim 1 and Q is



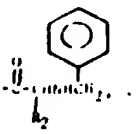
(wherein Hal is a halogen atom, R is substituted or unsubstituted alkyl, aralkyl or aryl group), provided that

a) when Q is



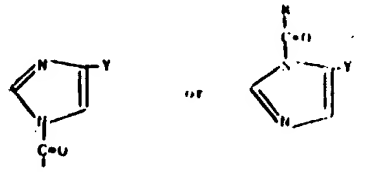
the reaction with formamide is followed by treatment of the intermediate product with acid; and

b) when Q is



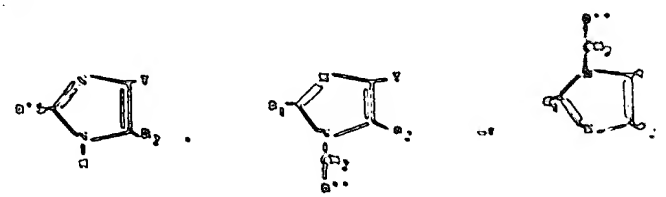
the reaction with formamide is followed by hydrogenation of the intermediate product.

74. A process for the preparation of a compound as claimed in Claim 1 which comprises hydrolysing a compound of the formula



where Y is the arylalkyl residue determined by the formula (I) and (II), R is an alkyl group of 1 to 7 carbon atoms an aryl radical of 6 to 10 carbon atoms.

75. A process for the preparation of a compound as claimed in Claim 1 which comprises hydrogenating a compound of the formula

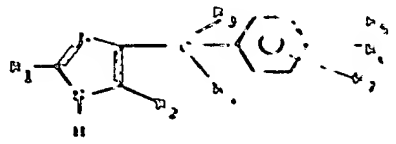


wherein Y is as defined in Claim 74, R' is an aryl or alkyl and R'' is an aryl group

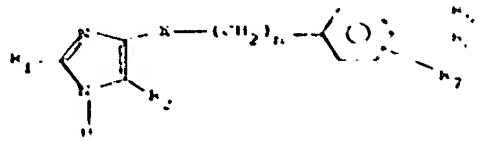
76. A process for the preparation of a compound as claimed in Claim 1 substantially as described in any one of the foregoing Examples.

77. A compound as claimed in anyone of Claims 1 to 60 when prepared by a process as claimed in anyone of Claims 64 to 75.

78. A substituted imidazole of the general formula



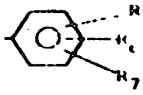
(I)



(II)

wherein R_1 is H, an alkyl of 1 to 4 carbon atoms or $-CH_2OH$; R_2 is H or CH_3; R_3 is

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $CH(CH_3)CH_3$, $-CH_2CH_2CH_2CH_3$,

$-CH_2CH=CH_2$, or  ; and R_4 is H or OH;

or R_3 and R_4 together represent $=CH_2$, $=CH-CH_3$,

$=CH-CH_2-CH_3$, $=C(CH_3)CH_3$, or $=CH-CH_2CH_2CH_3$; X is

$-CH(R_8)-CH(R_9)-$ or $-C(R_{11})=C(R_{10})-$; R_8, R_9 and R_{10}, which can be the same or different, and H, $-CH_3$, $-CH_2CH_3$, halogen, OH or $-OCH_3$ or R_8 is hydrogen and R_9 and R_{10} together form an O CH_2 O bridge between two adjacent carbon atoms in the phenyl group; $-CHR_8-$ is $-CH_2-$, $CH(CH_3)$,

$-CH(-CH_2CH_3)-$, $-CH(-CH_2CH_2CH_3)-$, $-CH(-CH(CH_3)CH_3)-$,

$-CH(-CH_2CH_2CH_2CH_3)-$ or $C=CH_2$, $C=CH-CH_3$, $C=CH-CH_2CH_3$.

$-CH_2CH_2CH_3$; $-CH(CH_3)-CH_3$, $-CH_2CH_2CH_2CH_3$ or CH_3, R_{10} is H, $-CH_3$,

$-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$, R_{11} is H,

$-CH_3$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $CH(CH_3)-CH_3$ or $-CH_2CH_2CH_2CH_3$,
n is 0 to 4, provided that R_9 and R_{10} or R_{11} and R_{12} are not simultaneously hydrogen, and its non-toxic pharmaceutically acceptable acid addition salts, for use in therapy as an antihypertensive agent, antithrombotic agent, antimycotic or antifungal agent.

79. A pharmaceutical composition comprising an imidazole derivative as defined in Claim 78 or a non-toxic pharmaceutically acceptable acid addition salt thereof and a compatible pharmaceutically acceptable carrier therefor.

80. A pharmaceutical composition comprising an imidazole derivative as claimed in any one of the Claims 1 to 63 or 77 or a non-toxic pharmaceutically acceptable acid addition salt thereof and a compatible pharmaceutically acceptable carrier therefor.

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